

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of:

Andreas Nandy et al.

Examiner: ROONEY, NORA
MAUREEN

Serial No.: 10/583,093

Group Art Unit: 1644

Filed: June 15, 2006

Confirmation No.: 1555

Title: **DNA SEQUENCE, AND RECOMBINANT PREPARATION OF THE GRASS
POLLEN ALLERGEN LOL P4**

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

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Sir:

Further to the Notice of Appeal filed September 22, 2009, attached is Appellants' Brief on Appeal, pursuant to 37 CFR §41.20(b)(2). An authorization to charge the requisite fee set forth under 37 CFR §41.20(b)(2) is also enclosed herewith.

This is an appeal from the decision of the Examiner finally rejecting claims 10-12 and 18-19 of the above-identified application under 35 USC §103(a). The final rejection was mailed on June 9, 2009.

(I) REAL PARTY IN INTEREST

Merck Patent GmbH of Darmstadt, GERMANY is the Assignee of Record of the entire right, title, and interest in and to the above-identified application, as recorded in the U.S. Patent and Trademark Office on June 15, 2006, at Reel/Frame 018016/0769.

(II) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(III) STATUS OF THE CLAIMS

Claims rejected: Claims 10-12, 18 and 19.
Claims allowed: (None).
Claims cancelled: Claims (None).
Claims withdrawn: Claims 1-9 and 13-17.
Claims on Appeal: Claims 10-12, 18 and 19. (Copy of claims on appeal in the attached Appendix).

(IV) STATUS OF AMENDMENTS

In the Claims Appendix section of this brief, the amendments presented with the non-final Reply of March 2, 2009 (to the Office Action of September 30, 2008) are entered and are reflected. New claim 20, which was added via the after-final reply but which was not entered, is not being reflected herein.

An amendment under 37 CFR 41.33(b)(2) is submitted herewith. Entry thereof is earnestly solicited.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

One aspect of Appellants' invention (independent claim 1) is directed to a polypeptide which is encoded by a polynucleotide which comprises the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3. See, for example, the disclosure contained in page 5, lines 20-32 of the originally-filed specification. Claims 11, 12 and 18 are directly or indirectly dependent on the aforementioned independent claim 10, and recite additional aspects of the product(s) of the instant invention. For example, claim 11 is directed to medicaments comprising a polypeptide according to claim 10 and an excipient or adjuvant. See, for example, page 9, lines 9-13 of the originally-filed specification. Claim 11 is directed to pharmaceutical compositions comprising at least one polypeptide according to Claim 10 and a pharmaceutically acceptable carrier. See, for example, the paragraph bridging pages 11 and 12 of the originally-filed specification. Claim 18 is directed to recombinant polypeptides which are encoded by the polynucleotides comprising the sequences set forth in SEQ ID NO: 1 or SEQ ID NO: 3. Support for the claim can be found in, for example, the paragraph bridging pages 7 and 8 of the specification and the disclosure contained in the Examples.

Another aspect of Applicants' invention (claim 19) is directed to an isolated polypeptide which is encoded by a polynucleotide having the sequence set forth in SEQ ID NO: 1 or SEQ

ID NO: 3. Support for the claim can be found in, for example, page 9, lines 5–7 and original claim 9 of the originally-filed specification. See also the disclosure contained in the Examples.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Appellants request a review of the following remaining grounds of rejection. For each ground, any separate grouping of the claims subject to that rejection is indicated. As per the requirements under 37 CFR §1.113(a), objections of formal nature are not being appealed.

- (1) The rejection of claims 10-12, 18 and 19 under §102(a) as allegedly anticipated by Bose (*Immunology*, 1998), Zhou (*Immunology*, 1995), Gefter (USP 6,759,234) or Gefter (WO 96/07428).
- (2) The rejection of claims 10-12, 18 and 19 under §112, first paragraph as allegedly lacking enablement.
- (3) The rejection of claim 10 under §101 as allegedly being directed to non-statutory subject matter.

Grouping of claims

Claims 10–12 and 18 stand or fall together with independent claim 10.

Claim 19, in its amended form, stands or falls independently of claim 10.

(VII) ARGUMENT

Rejections under §102

Claims 10-12, 18 and 19 are rejected under §102(b) as allegedly anticipated by Bose (*Immunology*, 1998), Zhou (*Immunology*, 1995), Gefter (USP 6,759,234) or Gefter (WO 96/07428). These rejections are not supported on the record as a whole and should be reversed.

The art rejections under §102 are based on the aforementioned references' disclosure of the terms "Lol p 4" and "allergen". The Office Action has not established that such allergens are structurally and/or biochemically identical to the polypeptide(s) encoded by SEQ ID NO: 1 or SEQ ID NO: 3, as claimed herein. More specifically, the totality of the disclosure in Bose (*Immunology*, 1998), Zhou (*Immunology*, 1995), Gefter (USP 6,759,234) or Gefter (WO 96/07428) says nothing about the amino acid sequences and the resulting allergenic property of the claimed molecules. Absent such, the references cannot anticipate what is claimed herein.

In the final rejection mailed June 9, 2009, the Examiner sustained this rejection alleging that the references' disclosure of "Lol p 4" anticipates the instantly claimed polypeptides. Applicants respectfully disagree that a generic characterization of a molecule by its name necessarily and inevitably meets all the elements of Applicants' claimed product(s). To this end,

posted below are results of the search report carried out on September 22, 2008, which was used in the non-final rejection mailed September 30, 2008. The top ten matching sequences are displayed:

| SUMMARIES | | | | | | |
|------------|--------|---------------|--------|----|----------|--------------------|
| Result No. | Score | % Query Match | Length | DB | ID | Description |
| 1 | 2264 | 95.9 | 423 | 10 | AEB13456 | Aeb13456 Lolium pe |
| 2 | 2264 | 95.9 | 500 | 10 | AEB13458 | Aeb13458 Lolium pe |
| 3 | 2119 | 89.7 | 500 | 8 | ADI44454 | Adi44454 P. praten |
| 4 | 2119 | 89.7 | 500 | 10 | AEB13460 | Aeb13460 Phleum pr |
| 5 | 2119 | 89.7 | 500 | 10 | AEB28062 | Aeb28062 Phleum pr |
| 6 | 2087 | 88.4 | 500 | 8 | ADI44452 | Adi44452 P. praten |
| 7 | 2087 | 88.4 | 500 | 8 | ADI44450 | Adi44450 P. praten |
| 8 | 1948 | 82.5 | 518 | 10 | AEB28056 | Aeb28056 Hordeum v |
| 9 | 1926.5 | 81.6 | 518 | 10 | AEB28052 | Aeb28052 Secale ce |
| 10 | 1921 | 81.3 | 518 | 10 | AEB28058 | Aeb28058 Triticum |

In the “alignment analysis” which follows the aforementioned table, it is further acknowledged that among these top-matching sequences, *only* the polypeptides encoded by AEB13456 (423 amino acids) and AEB13458 (500 amino acids) are identical to the instantly claimed polypeptide of SEQ ID NO: 2 and SEQ ID NO: 4, respectively. These reference polynucleotides are disclosed in WO 2005-058936 to Feibig et al. Coincidentally, WO 2005-058936 is the WIPO publication of the international application PCT/EP2004/013663 (PCT ‘663) and the present application is the US national phase of PCT ‘663. It is clear that none of the *other* sequences encode the claimed polypeptide sequence of SEQ ID NO: 2 or SEQ ID NO: 4. To this end, the next top-matching sequence of ADI44454 encodes a protein that has 96.2% sequence identity to the claimed SEQ ID NO: 4 (16 mismatches). See the “Alignment Scores” section of RESULT 3 in the search report of September 22, 2008. Thus it is clear, at least based on the results of the sequence search, that the claimed polypeptides are both novel and unobvious over the art-known proteins.

In the Advisory Action mailed September 21, 2009, the Examiner contends that “the disclosure of a polypeptide encoded by SEQ ID NO: 1 or 3 is only further characterization of an old product” and that “the references are not required to provide polypeptide sequences to anticipate the instant claims.” These contentions are respectfully traversed.

It is by now well-established that “a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” See MPEP §2131 and further corroborated by the Fed. Circuit’s decision in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). With respect to inherency, the Courts have established that “the extrinsic evidence ‘must

make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Inasmuch as the cited Gefter et al., Bose et al., Zhou et al, and WO 96/07428 say nothing about Lol p 4 polypeptide sequences and the art (or the Examiner) has not established that the Lol p 4 polypeptide disclosed therein necessarily comprises the sequences recited herein, the rejection is without legal merit.

With respect to the PTO’s contention that sequences need not be provided, the controlling case law dictates that for anticipation, “the identical invention must be shown in as complete detail as is contained in the ... claim.” *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The Office Action fails to establish that the polypeptides disclosed in the aforementioned references contain the **complete** Lol p 4 polypeptide sequence as presently claimed. To this end, Applicants enclose an exhibit (EXHIBIT A) which demonstrates that a search of the term Lol p 4 in NCBI’s protein database results in the identification of at least four Lol p 4 variants (accession Nos. CAH92637, CAJ18067, CAJ18069 and CAJ18068) and a fragment sequence (accession No. A60737). It cannot be ascertained whether the references teach a sequence that is completely different from what is claimed in the present application. More importantly, it is clear to those skilled in the art that none of the cited references of Bose, Zhou, Gefter (USP 6,759,234) and Gefter (WO 96/07428) provide “a complete detail” (i.e., the polypeptide sequence) of the claimed invention. As such, an inherency rejection under §102/§103 is not supported and should be withdrawn. See MPEP §2112.

Moreover, the Examiner has given no basis for alleging that it would be “reasonable” to assume that the references’ products are the same as those claimed herein. See *In re Best* 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). If anything, the record summarized above shows such an assumption to be unreasonable. Thus, the burden remains on the Examiner. Favorable action is earnestly solicited.

Claim 19

With respect to instant claim 19, Applicants respectfully submit that none of the references teach or disclose an isolated polypeptide having the claimed structural features. As such, like claim 10, the rejection of claim 19 under this section cannot stand.

Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, ¶1

Claims 10–12 are rejected due to allegedly lacking enablement with respect to the use of the polypeptides of the present invention as pharmaceutical compositions. This rejection is not supported on the record as a whole and should be reversed.

Enablement

In the paragraphs bridging pages 5 and 8 of the final Office Action, the Examiner alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

Applicants' specification, coupled with a skilled worker's knowledge, provides more than adequate guidance on how to make the claimed polypeptide molecules and use pharmaceutical compositions and medicaments comprising such polypeptides for immunotherapy. The specification provides both general and specific guidance regarding the specific epitopes in allergens and how such could be manipulated for reliable hyposensitisation. See, for example, the disclosure contained in the paragraphs bridging pages 6 and 7 of the instant specification and the reference article by Schramm et al., 1999, *J. Immunol.* 162: 2406-2414. With respect to DNA vaccines, the specification explicitly teaches that "experimental evidence of allergen-specific influencing of the immune response has been furnished in rodents by injection of allergen-encoding DNA (Hsu et al., 1996, *Nature Medicine* 2 (5): 540-544)." Furthermore, the specification of the present application discloses specific immunotherapy or desensitization as therapeutic field for especially recombinant allergen proteins with higher purity and therefore reduced side effects than allergen proteins isolated from natural sources which are always mixtures of compounds. To this end, the specification discloses strategies to minimize the risks of side effects with the development of T-cell reactive fragments with reduced or no IgE-reactivity leading to hypoallergenic peptides (see, page 8, lines 15–26). The screening for T-cell and IgE epitopes were common knowledge at the priority date of the present application. Thus, a person skilled in the art would have been able to identify T-cell and IgE epitopes and produce hypoallergenic peptides. Nevertheless, also the classic approaches of specific immunotherapy and desensitization were applicable as a skilled person would have known the pharmaceutical effects and also the side effects and risks of an allergen protein administered to a patient and would have followed clinical recommendation protocols for specific immunotherapy and desensitization.

In relation to an enabling disclosure on the utilization of grass pollen allergen

polypeptides in treatment of subjects, the specification provides a detailed disclosure for the design, synthesis and use of recombinant allergen extracts with reduced IgE reactivity. See, for example, the last paragraph on page 6 of the originally-filed specification. To this end, the Examiner is also courteously invited to review the disclosure contained in Focke et al., which was submitted with the previous Reply (Focke et al., *EASEB Journal*, 15, 2042-44, 2001). As evidenced by the disclosure in the “Principle Findings” section of Focke and the immunoglobulin reactivity data provided in Table 1, it is respectfully submitted that as of the filing date of the present application, the instantly claimed grass pollen allergens could be routinely manipulated and utilized as pharmaceutical preparations in a manner recited in the claims.

Thus it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the recombinant, grass pollen allergen polypeptides of the instant invention. Therefore, the specification’s express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO’s contentions regarding non-enablement are especially weak in view of the detailed disclosure contained in Applicants’ own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

To support the contention of non-enablement, the Office Action cites Tarzi (*Expert Opinion in Biol. Ther.*, 2003) to allege that “whole allergen immunotherapy is unpredictable.” However, even Tarzi discloses the therapy of allergic diseases with specific immunotherapy or desensitization in general being effective and successfully applied for many years. See, the last paragraph at page 617 of the cited reference. Moreover, in Gefter et al. (USP 6,795,234), which was cited by the PTO in reference to an art rejection, the complete third and fourth paragraphs in the “BACKGROUND OF THE INVENTION” (especially, col. 1, lines 26–45) discloses that the risk of systemic reactions like anaphylactic shock can be effectively minimized in individuals via specific immunotherapy, wherein pharmaceutical compositions comprising allergen polypeptides and/or vaccines comprising DNA sequences which encode such polypeptide allergens are utilized. As such, the PTO’s contentions of non-enablement, based on the disclosure contained in Tarzi and/or Gefter is without merit.

The final Office Action at page 6 alleges that it would “take undue trials and errors to practice the claimed invention.” These allegations, however, do not present any evidence to doubt the objective enablement of Appellants’ disclosure. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

Furthermore, as stated in *Marzocchi*, at 370, the PTO must have adequate support (evidence or reasoning) for its challenge to the credibility of Appellants' statements of enablement. Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the requirements of 35 U.S.C. § 112, ¶1.

Working examples are not required to establish enablement. As stated by the court *Marzocchi*, at page 369:

The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The assertion of undue experimentation in the rejection is merely conclusory. Further, as discussed above, the specification provides more than sufficient guidance to make and use the claimed medicaments and/or pharmaceutical compositions using no more than routine experimentation. Finally, a high level of skill does not establish that one skilled in the art would have reasons to doubt the veracity of the statements in Appellants' specification with respect to the use of the claimed composition in the diagnosis, treatment, and/or prevention of the claimed conditions.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

Rejections under §101

The rejection of claim 10 under §101 is respectfully traversed.

Applicants respectfully disagree with the Examiner's contention that that the polypeptide encoded by the polynucleotide SEQ ID NO: 1 or SEQ ID NO: 3 could exist in nature. The disclosure in page 5, lines 25–32 of the instant specification expressly teaches that the "DNA sequence (SEQ ID NO 3) [is] composed of nucleotides 1-200 of Phl p 4 (in

accordance with SEQ ID NO 5), 201-1472 of Lol p 4 (in accordance with SEQ ID NO 1) and 1473-1503 of Phl p 4 (in accordance with SEQ ID NO 5).” As such, any skilled worker can appreciate that the polynucleotide sequence set forth in SEQ ID NO: 3 and the protein encoded thereby are not naturally-occurring. Withdrawal of the rejection is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Date: December 22, 2009

(VIII) CLAIMS APPENDIX

Claim 10. A polypeptide which is encoded by a polynucleotide which comprises the sequence set forth in SEQ ID NO: 1 or SEQ ID NO: 3.

Claim 11. A medicament which comprises a polypeptide according to claim 10 and an excipient or adjuvant.

Claim 12. A pharmaceutical composition comprising at least one polypeptide according to Claim 10 and a pharmaceutically acceptable carrier.

Claim 18. The polypeptide according to claim 10, which is a recombinant polypeptide.

Claim 19. The polypeptide according to claim 10, which is an isolated polypeptide.

(IX) EVIDENCE APPENDIX

Appendix of evidence submitted pursuant to §§ 1.130, 1.131, or 1.132 of this title or of any other evidence entered by the Examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered in the record by the Examiner. Copies of the evidentiary documents are attached.

| Reference/Exhibits | Entered in the Record |
|--|--|
| 1. Bose et al., “Human and murine antibodies to rye grass pollen allergen LolpIV share a common idiotope.” <i>Immunology</i> , 1988 April; 63(4): 579–584. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 2. Zhou et al., “Regulation of levels of serum antibodies to ryegrass pollen allergen Lol pIV by an internal image anti-idiotypic monoclonal antibody.” <i>Immunology</i> , 1995 March; 84(3): 343–349. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 3. Zhou et al., “Antibody responses to allergen Lol pIV are suppressed following adoptive transfer of B lymphocytes from the internal image anti-idiotypic antibody-treated mice.” <i>Cell Immunol.</i> 1995 Oct 1;165(1):77-83. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 4. Gefter et al., “Peptide compositions capable of down-regulating an antigen-specific immune response.” WO publication No. 96/07428. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 5. Gefter et al. “Compositions and methods for administering to humans, peptides capable of down-regulating an antigen-specific immune response.” US Patent No. 6,759,234. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 6. Tarzi et al. “Peptide immunotherapy for allergic disease.” <i>Expert Opin Biol Ther.</i> 2003 Jul;3(4):617-26. | Cited by the Examiner in the Office Action mailed September 30, 2008. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the Office Action mailed June 9, 2009. |
| 7. Exhibit A. NCBI Protein Database Search of the term “Lol p 4.” (Declaration under §1.130, §1.131 or §1.132). | Provided by the Appellant in the Reply filed September 4, 2009. A copy of the Exhibit was provided and entered on the record. Acknowledged by the Examiner in the Advisory Action mailed September 21, 2009. |

(IX) EVIDENCE APPENDIX (CONTD)...

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| <p>8. Focke et al. "Nonanaphylactic synthetic peptides derived from B cell epitopes of the major grass pollen allergen, Phl p 1, for allergy vaccination." The FASEB Journal. 2001; 15: 2042-2044.</p> | <p>Cited by the Applicant in the Reply filed March 2, 2009. The Office Action mailed June 9, 2009 acknowledges this reference. A copy of the reference was provided and entered on the record. Reliance thereon maintained in the After-Final Response.</p> |
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(X) RELATED PROCEEDINGS APPENDIX

(None)